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10/599,401	02/27/2007	Seth Hallstrom	16785.10	8352

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EXAMINER
LIU, SAMUEL W

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,401	HALLSTROM ET AL.	
	Examiner	Art Unit	
	SAMUEL LIU	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-18* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,2 and 4-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 March 2010* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/14/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

Claims 1, 2, and 4-18 are pending.

The amendment filed 3/16/10 which amends claims 1, 2, and 4-18 has been entered. Claims 1, 2, and 4-18 are under examination.

Withdrawal of objection and rejection

[1] The objection of the specification is withdrawn in light of the amendment of the specification thereof.

[2] The 101 rejection of claims 1-18 is withdrawn in light of cancellation of claim 3 and the amendment of claim 1, 2 and 4-18.

New-Objection to the specification

The specification as originally field and the amended specification filed 3/16/10 do not provide the brief description for Figure 4.

IDS

The references cited in the information disclosure statement (IDS) filed 10/14/09 which can be found in the parent application 10871752 have been considered by Examiner.

Objection to claims

Claims 1, 2, and 4-18 are objected to because in claim 1 "having an average molecular weight of at most 10000" should be changed to "having a molecular weight of less than 10000", since "average molecular weight" cannot be followed by a unlimited lower-range and should associate with a definite number. Suggest placing the units as well, 10,000 Da or g/mol.

Claim 6 remains objected to as "wherein a compound" should be changed to "wherein the compound"

Claim 8 remains objected to as containing non-elected subject matters "S-nitroso orosomucoid, S-nitroso plasminogen activator, S-nitroso fibrinogen, S-nitroso Lys-plasminogen and S-nitrosohaemoglobin".

Claim 13 remains objected to as containing non-elected subject matters "L-cysteine, N-acetyl cysteine, L-cysteinyl glycine, γ-glutamyl cysteine, penicillamine, penicillamide, N-acetyl penicillamine, N-acetyl penicillamide, homocysteine, captopril, dihydrolipoic acid".

Claims 14-18 remain objected becasue in claims 14-15, "wherein a therapeutic protein" should be changed to "wherein the therapeutic protein" for the reason that claim 1 from which claims 14-15 has set forth "therapeutic protein"; similarly, see also claims 16-18.

Maintained-Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 11-13 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 remains rejected because claim 9 should make it clear whether or not "the oxidized form thereof" only refers to "dihydrolipoic acid" and/or any other thiol-containing compound(s) set forth in the Markush group of claim 9. Claims 12-13 which depend from claim 9 are also rejected.

Claim 11 lacks antecedent basis for "reduced glutathione" because neither claim 8 nor claims 1 or 2 from which claim 11 depends sets forth the "reduced albumin".

Maintain-Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2 and 4-18 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Schlag et al. (US Pat. No. 6358918 B1) in view of Tsikas et al. (*Biochem. Biophys. Acta* (2001) 1546, 422-434) and Hallstrom et al. (2002) *Circulation*, 105, 3032-3038).

In patent claims 16-18 and 21, Schlag et al, teach a method of treating an ischemia (cerebral ischemia) comprising administering to a patient in need thereof a pharmaceutical composition comprising at least one thiol nitrosated (i.e., S-nitroso) thiol-group-containing proteins, wherein "at least one" encompasses more than one S-nitroso-proteins that include S-nitroso-albumin (patent claims 21). The composition may comprise a low-molecular weight protein, e.g., glutathione (col.2, lines 61 and 62) which is a thiol-containing compound with

molecular weight less than 10,000" as set forth in instant claim 1. Since the disclosed protein as free thiol group (col.2,lines 23-34), Said "glutathione" refers to a reduced glutathione. These are applied to instant claims 1, 4, 5, and 10.

At least 95% of the thiol-group-containing proteins are S-nitrosated (patent claim 19) while N-nitrosation, O-nitrosation and/or C-nitrosation level is less than 10% (patent claim 24). This is applied to instant claims 2, 7 and 14-18 and claims 9, 11 and 12.

The glutathione occurs in human blood (col. 1, lines 48-56), as applied to instant claims 6 and 13.

Schlag et al. do not expressly disclose or provide working example for combined use of S-nitroso-albumin (S-NO-HSA) and S-nitroso-glutathione(GSH) for the treatment of an ischemia.

Schlag et al. et al., however, teach the increased S-nitrosation level for the higher the "NO-coupled effect" when administering a nitrosated protein preparation comprising such the increased S-nitrosation level (col. 2, lines 23-34), wherein said nitrosated protein is SNO-ALB (patent claim 21), and wherein the "NO-coupled effect", in the relative art, refers to high level of nitric oxide (NO) production during ischemia followed by increasing release of O_2^- thereby increasing endothelial ischemic damage (p.3032, left col., lines 1-2, and right col., lines 10-14, Hallstrom et al.).

Schlag et al. teach that a near complete S-nitrosation of albumin is preferred, e.g., > 95% S-nitroso albumin (see patent claims 16, 17, 19 and 21, and col.3, lines 5-6). Also Schlag et al. et al. teach use of thiol-group containing protein (encompassing GSH) for formulating a pharmaceutical composition for treating the ischemia (col.6, lines 56-63).

Tsikas et al. teach that S-transnitrosylation of albumin by S-nitroso-glutathione (GSNO) is the most favored and most efficient mechanism for producing the S-nitroso albumin (S-NO-HSA) in vivo and in vitro (see abstract and page 423, left col., lines 19, "formula (1)", and right col., lines 17-21).

These teachings are applicable to claim 1 and dependent claims therefrom.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use S-nitroso albumin and S-nitroso GSH together for treating the ischemia. This is because of the reasons below.

The S-NO-HSA treatment of skeletal muscle against ischemia/reperfusion is a powerful tool in preventing or reducing the ischemia/reperfusion thereof (p. 3038, last paragraph, Hallstrom et al.). Schlag et al. have taught that the higher S-nitrosation level of albumin is proportional to the higher the "NO-coupled effect". Said effect refers to that NO gradually released by S-nitroso albumin (S-NO-HSA) actively scavenges superoxide (O_2^-) wherein O_2^- contributes to ischemia/reperfusion injury (p. 3033, left col., lines 1-17, and abstract, Hallstrom et al.). The best way to achieve/maintain high level of the S-NO-HSA would be addition of the S-nitroso GSH with the S-nitroso albumin, since the S-nitroso GSH (**GS**NO) assisted S-transnitrosylation of albumin is the most favored and most efficient mechanism for formation of the S-nitroso albumin (S-NO-HSA), as taught by Tsikas et al. (see above). Experimental data have shown that infusion of GSNO in the rat results in formation of S-nitrosated albumin (S-NO-HSA), and thus, suggested that *S*-transnitrosylation of albumin by GSNO could be a more favored mechanism for the formation of in the circulation in vivo than *S*-nitrosation of albumin by NO itself (see abstract, Tsikas et al.).

Upon reading the Schlag, Tsikas and Hallstrom references, one of ordinary skill in the art would have readily recognized importance and benefit of inclusion of the S-nitroso GSH (GSNO) and would have tried formulation of GSNO with S-NO-HSA for treating ischemia state. When tried, it would have led to reasonable expectation of success. Therefore, the combination of the references' teachings renders the claimed invention *prima facie* obvious in the absence of unexpected result.

The applicants' response to the 103(a) rejection

At pages 14-16, the response filed 3/16/10 argues that Schlag et al. do not teach the pharmaceutical composition comprising "the compound containing thiol group and having an average molecular weight of at most 10,000" set forth in claim 1 (page 14, last paragraph to page 15, 1st paragraph, and page 16, 2nd paragraph).

The response submits that Tsikas is silent in teaching treatment of ischemia and in teaching a combined preparation of S-nitroso albumin with a compound containing thiol groups with an average molecular weight of not more than 10,000 (page 15, 2nd paragraph).

The response submits that while Hallstrom has taught usefulness of S-nitroso human serum albumin in treatment of skeletal muscle ischemia injury, this reference does not suggest the combined preparation of S-nitroso human serum albumin (S-NO-HSA) with the "compound" containing thiol groups with an average molecular weight of not more than 10,000 (page 15, 3rd paragraph). Similarly, the response asserts that the combination of Schlag, Tsikas and Hallston does not teach the claimed method using S-NO-HSA and said "compound" (e.g., GSH) together for the treatment, and that Tsikas is silent in treating ischemia (page 15, last paragraph to page

16, 1st paragraph). Thus, the response infers that the combination of the 103 references does not render the claims *prima facie* obvious; and therefore, request withdrawal of the rejection (page 16, 3rd paragraph).

The applicants' arguments are found unpersuasive because of the reasons set forth in the above rejection and the reasons below. Schlag et al. have taught use of the pharmaceutical composition comprising S-nitroso albumin (S-NO-HSA) for treating the ischemia, and have suggested that said composition comprises at least one thiol-group-containing proteins (multiple proteins) which would encompass not only S-NO-HSA but also glutathione reduced form. Here, the glutathione is the compound "containing thiol groups with an average molecular weight of not more than 10,000" (see instant claim 4).

Tsikas et al. have taught the best way to achieve/maintain high level of the S-NO-HSA through formulation of it with GSH, since the S-nitroso GSH (**GS**NO) assisted S-transnitrosylation of albumin is the most favored and most efficient mechanism for formation of the S-nitroso albumin (see above). While Tsikas et al. do not expressly use of both S-NO-HSA and GSH for treating the ischemia, the nexus between said use and said treatment has been taught and provided by the teaching of the primary reference Schalag (see above).

The *S*-transnitrosylation of albumin (resulting S-NO-HSA) by S-nitroso GSH is the more favored and the most efficient mechanism for the formation of in the circulation in vivo than *S*-nitrosation of albumin by NO itself (see the corresponding teaching of Tsikas et al.). Thus, one of ordinary skill in the art would have not ignored said "more favored" and "most efficient", and would have formulated S-nitroso albumin having SH-group with GSH in order to

achieve/maintain the high level of S-NO-HSA which actively scavenges superoxide (O_2^-) that causes the ischemia or ischemia/reperfusion injury.

Although Hallstrom et al. do not teach the limitation as to the thiol "compound" having molecular weight of at most (i.e., less than) 10,000 (e.g., GSH), this reference provides teaching/motivation that the composition comprising the S-nitroso albumin is a powerful tool for treating the ischemia. The obviousness of achieving and maintaining the high level of the S-nitroso albumin in the presence of the GSH has been discussed *supra*.

Thus, it would have been obvious for one of ordinary skill in the art to formulate the S-nitroso albumin having thiol groups with the GSH for the ischemia treatment with reasonable expectation of success. Therefore, the 103(a) rejection is deemed proper and maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Liu whose telephone number is (571)272-0949. The examiner can normally be reached on Monday-Friday, 9 am to 5:30 pro. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Samuel Wei Liu/
Patent Examiner, Art Unit 1656

/ANAND U DESAI/
Primary Examiner, Art Unit 1656
June 18, 2010